REMARKS

Claims 1-13, 16-17, 23-29 and 33-47 are pending. Claims 14, 15, 18-22 and 30-32 have been canceled. Claims 1, 13 and 24-29 have been amended. New claims 34-49 have been added. Support for the amendments and new claims can be found throughout the application as originally filed. No new matter has been added.

Rejection of Claims 25 and 29-33 Under 35 U.S.C. §112, first paragraph

Claims 25 and 32 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner asserts

> The claims read on a broad genus of bacterial origins or replication fragment that can be used upon the removal of an undisclosed portion of the bacterial origin of replication. ... Applicant claims the use of a bacterial origin of replication fragment by function only, without any disclosed or known correlation between the elements and their function. The specification does not teach what portions of the bacterial origin of replication can be removed and result in retention of its function. Furthermore, the instant specification does not teach what portion of any bacterial origin of replication is absolutely necessary for it to function in the vector as claimed ... Neither the specification of the instant application nor the prior art teaches a structure-function relationship for a representative number of functional fragments of a bacterial origin of replication.

Claims 25 and 32 have been canceled, thereby obviating this rejection.

Claims 29-33 are also rejected under 35 U.S.C. §112, first paragraph, " as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner asserts that

> Applicant claims a viral vector that can express a heterologous insert sequence that is greater than 8 kb in length by function only, without any disclosed or known correlation between the elements and their function. The specification

does not teach what structural features of a vector permit the expression of insert sizes that are greater than 8 kb in length. There is no correlation between the particular vectors, or a feature therein, and the ability to express a sequence of greater than 8 kb in length recited in the specification. Thus, a skilled artisan would have no way of discerning which viral vectors would have this functional property by observing the features of the vector. As a result, the skilled artisan cannot envision a sufficient number of viral vectors that can express a heterologous insert sequence that is greater than 8 kb in length from the instant specification.

Applicants respectfully traverse this rejection. Claim 29 and its dependencies are directed to a viral vector that includes a packaging sequence, a heterologous insert sequence, a selectable bacterial marker that is less than 600 basepairs in length and a 3' UTR that includes proviral recovery sequence. The packaging sequence has at least two codons altered so as to reduce formation of fusion polypeptides of the packaging sequence and a portion thereof and the heterologous insert sequence. The vector includes and can express a heterologous insert sequence greater than about 8 kb in length. Thus, contrary to the Examiner's assertions, the claims recites several structural elements including the recited packaging sequence, a heterologous insert sequence greater than about 8 kb in length, a 3 'UTR that includes a proviral recovery sequence and a selectable bacterial marker of less than 600 kb. As such, Applicants have provided several structural features that result in a vector that can express a heterologous insert sequence greater than 8 kb. The Examiner's statement that " a skilled artisan would have no way of discerning which viral vectors would have this functional property by observing the features of the vector" is simply incorrect. The claim clearly provides several structural features in order to provide a vector that can express an insert sequence of the recited length. Thus, a skilled artisan could easily determine if a vector had the recited elements. Moreover, a skilled artisan, using routine skill, could easily determine if a vector having the recited elements expresses the heterologous insert sequence. Applicants were clearly in possession of the claimed invention at the time of filing, and therefore, respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 1-33 Under 35 U.S.C. §112, second paragraph

Claims 1-33 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In particular, the Examiner asserts that "claim 1 recites the limitation 'or a portion thereof' ... there is insufficient antecedent basis for this limitation in the claim."

Claim 1 has been amended to remove the phrase "or a portion thereof", thereby obviating this rejection.

Claims 13, 28 and 29 are rejected based upon the term "proviral recovery sequence". The Examiner asserts that "it is unclear what the limitation is intended to mean."

Applicants respectfully traverse this rejection. However, in the interest of expediting prosecution, Applicants have amended the claims to recite that the proviral recovery sequence is selected from at least one recombinase site, at least one rare cutter restriction site, and combinations thereof. The amendments obviate this rejection.

Claims 24-27 are rejected as having "insufficient antecedent basis for" the limitation "viral vector". Claims 24-27 have been amended to recite a "vector", thereby obviating this rejection.

The Examiner further rejects claim 26 as lacking sufficient antecedent basis for the limitation "the bacterial marker sequence." Claim 26 has been amended to obviate this rejection.

Claims 26, 28 and 29 are rejected as reciting "the limitation 'bacterial marker' without defining the term 'bacterial marker'." The Examiner asserts that "it is unclear if the bacterial marker represents a selectable marker ... or if bacterial marker sequence is meant to also include sequences that are specific to bacteria that can be used as an identification marker (e.g., by Southern Blot)."

Applicants have amended the claims to recite "a selectable bacterial marker", thereby obviating this rejection.

Rejection of Claims 13, 16, 17, 23, 27 and 28 Under 35 U.S.C. §102(b)

Claims 13, 16, 17, 23, 27 and 28 are rejected under 35 U.S.C. §102(b) "as being anticipated by Bender *et al.*" According to the Examiner,

> Bender teaches a retroviral vector comprising a 5' LTR, the packaging sequence (a.k.a., psi) from Moloney Murine Leukemia Virus (henceforth MoMuLV), a heterologous insert sequence consisting of a bacterial selection marker less than 600bp in length (e.g., hygromycin/hph gene), and a 3' LTR (see for example Figure 1 and page 1640, left column, first complete paragraph). Bender also teaches adding an amino terminal portion of the MoMuLV gag sequence, mutated at its initiation ATG codon, to the packaging sequence, and that this addition increases the titer ... of the vector (see for example page 1642, right column, bridging paragraph). Therefore, Bender anticipates a viral vector comprising a packaging sequence (psi/gag amino terminus fusion) with at least one ATG codon altered, a heterologous insert sequence (hph) that is a bacterial marker sequence of less than 600 basepairs in length, and a proviral recovery sequence (LTR).

Applicants respectfully traverse this rejection. The claims, as amended, are directed to a vector that includes a packaging sequence having at least one ATG codon that has been altered, a heterologous insert sequence or restriction sites for insertion of a heterologous sequence, and a 3' UTR that includes proviral recovery sequence selected from at least one recombinase site, at least one rare cutter restriction site and combinations thereof.

Bender et al. do not teach or suggest a vector having a 3'UTR having a proviral recovery sequence selected from at least one recombinase site, at least one rare cutter restriction site and combinations thereof. Thus, Bender et al. do not teach or suggest every element of the claims and, therefore do not anticipate the claimed invention.

Rejection of Claims 1-5, 7, 11, 12-18, 22-23 and 27 Under 35 U.S.C. §102(e)

Claims 1-5, 7, 11, 12-18, 22-23 and 27 are rejected under 35 U.S.C. §102(e) "as being anticipated by Kingsman et al. (US Patent No. 6,235,522)". According to the Examiner,

Kingsman teaches a retroviral vector comprising a 5' LTR, a portion of the HIV1 gag packaging sequence gene (specifically nucleotides 791-1143 of the full length sequence, which corresponds to the amino-terminal region of HIV gag) altered at its three ATG codons (including the gag initiator codon, a multicloning site (comprising a number of restrictions sites for insertion of a heterologous gene), and a 3' LTR (i.e., a proviral recovery sequence).

Applicants respectfully traverse this rejection. Kingsman et al. do not teach or suggest a vector that includes a proviral recovery sequence selected from at least one recombinase site, at least one rare cutter restriction site and combinations thereof. Thus, Kingsman et al. do not teach or suggest every element of the claims, and therefore do not anticipate the claimed invention.

Rejection of Claims 24, 26, 28, 29, 31 and 33 Under 35 U.S.C. §103(a)

Claims 24, 28, 29 and 31 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Beach et al (US Patent No. 6,255,071 ...) in view of Bender." According to the Examiner,

Beach teaches a retroviral vector comprising, a 5' LTR, a packaging sequence from MoMuLV (e.g., psi), a polylinker site (i.e., restriction sites for cloning of heterologous sequences), a bacterial origin of replication, and any bacterial selection marker ... Significantly, Beach also teaches what is referred to as a "proviral excision element" ... which includes the use of recombinase sites and rare-cutting restriction enzymes ... Absent any evidence to the contrary or any indication of what structural/functional features of a vector prevent or allow expression of an 8kb heterologous insert sequence ..., the vector that Beach teaches is considered to be capable of expressing a heterologous insert of greater than 8kb in length. However, Beach does not teach the alteration of at least one ATG codon in the packaging sequence.

Bender teaches the same elements as set forth in the rejections under 35 U.S.C. 102(b). Briefly, Bender teaches that the addition of the amino terminal portion of the MoMuLV gag sequence, with its initiator ATG codon altered, to the MoMuLV packaging sequence (i.e., psi) increases viral titer of a viral vector.

... The ordinary skilled artisan would be motivated to add the feature of an amino terminal MoMuLV gag sequence with its initiator ATG altered (taught by Bender) to the vectors taught by Beach because the addition of this sequence increases the titer of the viral vector (as Bender teaches), and it is desirable to obtain a vector having the highest effective level of infectivity.

Applicants respectfully traverse this rejection. As acknowledged by the Examiner, Beach et al. do not teach or suggest alteration of at least one ATG codon in the packaging sequence. Moreover, as discussed above, Bender et al. do not teach or suggest a vector that includes a proviral recovery sequence selected from a recombinase site (or sites), a rare cutter restriction site (or sites), or combinations thereof. Thus, neither Beach et al. nor Bender et al. teach or suggest the claimed invention.

The Examiner asserts that a skilled artisan would be motivated to combine a MoMuLV gag sequence having an altered ATG codon of Bender et al. with the vector of Beach et al. "because the addition of this sequence increases the titer of the viral vector (as Bender teaches)." However, in asserting this motivation, the Examiner mischaracterizes the teachings of Bender. Bender et al. does not teach or suggest that a gag sequence having an altered ATG codon increases titer as compared to an unaltered gag sequence. Bender et al. disclose that retroviral vectors containing the complete packaging signal allow for more efficient gene transfer into a variety of cell types. Specifically, Bender et al. produced vectors that include a portion of the gag region of MoMuLV. Bender et al. disclose that vectors that include this unmutated portion of the gag region result increased amounts of vector RNA secreted by virus producing cells. See, e.g., page 1639, column 2, first full paragraph. Bender et al. further mutate various portions of the gag sequence to determine if the increase in RNA produced results from "potential gene products expressed from the gag region" and conclude that "there was no difference in virus production from cells containing either mutation compared with that from cells containing the parental virus." Thus, Bender et al. disclose that the presence of an unmutated gag sequence increases titer and the increase is not due to the synthesis of some gag-related protein. Therefore, there is nothing in Bender et al. that teaches or suggests replacing an unmutated gag sequence (as disclosed by both Beach et al. and Bender et al.) with a gag sequence containing a mutated ATG codon. There is nothing in Bender et al. that teaches that a gag sequence having a mutated ATG codon is better than the unmutated gag sequence used in the vector of Beach et al. Therefore, even if the teachings of Beach et al. and Bender et al. are combined, there is nothing in either

reference that would motivate a skilled artisan to provide a packaging sequence having at least one altered ATG codon.

The teachings of Beach et al and Bender et al., alone or in combination, do not teach or suggest the claimed invention.

The Examiner further rejects claims 26 and 33 under 35 U.S.C. §103(a) "as being unpatentable over Beach in view of Bender as applied above ..., and in further view of Luo et al. (US Patent No. 6,114,111)."

Applicants respectfully traverse this rejection. As discussed above, neither Beach et al. nor Bender et al., alone or in combination, teach or suggest the claimed invention. Luo et al. do not make up for the deficiencies of Beach et al. and Bender et al. Therefore, the claimed invention is patentable over these references.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Enclosed are a check for excess claim fees and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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